Original Article
Association between left ventricular end-diastolic pressure and coronary artery disease as well as its extent and severity

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Abstract: Patients with myocardial ischemia exhibit increased left ventricular end-diastolic pressure (LVEDP). The study was to evaluate the relationship between LVEDP measured by left cardiac catheterization and coronary artery disease (CAD) as well as its extent and severity evaluated by coronary angiography (CAG). 912 patients who underwent CAG and left cardiac catheterization were enrolled. There were 313 patients without CAD and 599 with CAD according to CAG. The extent and severity of coronary artery was evaluated by number of vessels and Gensini score. Analyze the correlation of LVEDP and CAD as well as its extent and severity. LVEDP was significantly higher in CAD patients than non-CAD (9.58 ± 5.78 mmHg vs 10.9 ± 5.46 mmHg, $P<0.001$), and was correlated independently with the presence of CAD (OR = 0.11, per 5 mmHg increase, 95% CI 1.02-1.29, P = 0.02). LVEDP was increased with an increase of number of vessels. By linear regression analysis, LVEDP was significantly associated with Gensini score (standardized β = 0.034, P = 0.001). In non-CAD group, LVEDP was only correlated with age (r = 0.123, P = 0.030). In conclusion, our findings suggest that elevated LVEDP was significantly associated with CAD as well as its extent and severity. LVEDP was only correlated with age in non-CAD patients. LVEDP measurement provides incremental clinical value for CAD and non-CAD patients.

Keywords: Coronary artery disease, left ventricular end-diastolic pressure, Gensini score

Introduction

In the whole world, coronary artery disease (CAD) is one of major cause of mortality [1]. Ischemia can result in systolic dysfunction and diastolic dysfunction (DD). Diastolic dysfunction results in ineffective left atrial emptying and left ventricular filling, and reduces ability to augment cardiac output with exercise, increases in pulmonary pressure, and results in symptoms and fluid retention. The significance of systolic dysfunction on CAD is well recognized, increasing the rate of major adverse cardiovascular events [2]. In patients with CAD but normal left ventricular ejection fraction, often accompanying shortness of breath, decrease of quality of life [3]. As research progressed, DD is an increasing concern. DD affects the mortality rate and hospitalization significantly, resulting in the development of heart failure,

death and hospitalization evidently [4, 5]. Diastolic relaxation and filling appear to be altered by ischemia, which lead to asynchronous myocardial relaxation and thus affect global diastolic function. Diastolic function seems more susceptible to ischemia than systolic function and can take longer to recover [6]. AP in Heart failure with preserved ejection fraction (HFpEF) patients with a history of coronary artery disease is common despite medical therapy and previous revascularization, and it is independently associated with increased MACE due to revascularization, with similar risk of death, MI, stroke, and hospitalization [7]. Left ventricular diastolic function (LVDF) can be characterized by invasive and noninvasive methods. Although echocardiography is currently the method by which diastolic dysfunction is diagnosed, this method is prone to poor acoustic windows and suboptimal spatial reso-

Table 1. Comparisons of patients with and without CAD

	Non-CAD (n = 313)	CAD (n = 599)	P
Male (%)	44.7	61.1	<0.001
Age (years)	58.32±11.12	62.41±10.32	<0.001
Hypertension (%)	37.1	44.5	0.031
Diabetes mellitus (%)	8.3	18.8	<0.001
BMI (Kg/m^2)	24.57±5.56	24.87±3.99	0.675
TC (mmol/l)	4.84±1.08	4.92±1.20	0.361
TG (mmol/l)	1.52 (1.10-2.24)	1.63 (1.12-2.47)	0.063
LDL-C (mmol/l)	2.93±0.87	3.02±0.94	0.203
HDL-C (mmol/l)	1.32±0.39	1.21±0.34	<0.001
Serum creatinine (μmol/L)	78.26±15.57	82.68±25.49	0.011
Serum uric acid (μmol/L)	301.44±113.06	335.37±112.83	<0.001
Hemoglobin level (g/l)	137.38±17.71	135.18±29.9	0.128
RDW (fl)	45.12±4.51	46.68±18.79	0.164
PDW (fl)	16.28±0.43	16.32±0.53	0.281
LVEDP (mmHg)	9.58±5.78	10.9±5.46	<0.001
Gensini score	2 (0-5)	30.5 (15-60.8)	<0.001

lution [8]. Non-invasive survey of left ventricular end-diastolic pressure (LVEDP) by transmitral Doppler echocardiography and tissue Doppler imaging carries important information about left ventricular diastolic function in chosen subsets of patients. But the sensitivities and specificities of these methods are not very high [9].

To date, there is no research involving the relationship between left ventricular end-diastolic pressure (LVEDP) measured by left cardiac catheterization [3] and CAD as well as its extent and severity evaluated by coronary angiography (CAG). The present study was designed to investigate the relationship between the extent and severity of coronary lesions and left ventricular diastolic function in patients with coronary heart disease, and discuss the clinical incremental value of LVEDP.

Method

Study design and subjects

912 patients with clinical suspicion of CAD who underwent CAG and left cardiac catheterization between Jun 2011 and Dec 2012 in the First Affiliated Hospital of He'nan Science and Technology University were enrolled in this study. Major exclusion criteria included patients existing previous and acute myocardial infarction, congestive heart failure, hypertrophic cardiomyopathy, valvular heart diseases and con-

genital heart disease. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Henan Science and Technology University Written informed consent was obtained from all participants.

Collect the clinical date containing age, sex, hypertension (blood pressure ≥140/90 mmHg or the use of antihypertensive drugs), and diabetes mellitus (fasting plasma glucose ≥7.0 mmol/L or random plasma glucose ≥11.1 mmol/L or patients was on anti-diabetic medications), Body Mass Index (BMI) = body weight (kg)/ body height^2 (m^2), total cholesterol (TC), blood triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), hemoglobin level, red blood cell distribution width (RDW), platelet distribution width (PDW), LVEDP and the outcomes of CAG.

LVEDP measurement and coronary angiographies

LVEDP was measured according to the left cardiac catheterization. All LVEDP was measured just before contrast injected into the left ventricular or coronary artery. Selective coronary angiographies were performed via right or left radial artery according to standard Judkins techniques. The procedure of CAG and left cardiac catheterization were all performed by experienced interventional physician. CAD has been evaluated by CAG based on maximal luminal narrowing of visual stenosis and defined as the presence of at least one stenosis 50% or more in at least one of 15 coronary segments of the three major coronary arteries [10], if not, was diagnosed as non-CAD. The left anterior descending artery, left circumflex artery, and right coronary artery with luminal stenosis 50% or more were examined to evaluate the number of stenotic coronary arteries as 0 to 3-vessel disease. If the left main trunk was involved, this was evaluated as a 2-vessel disease by itself. The extent of CAD (vessels score) was coded as

Table 2. Comparisons of patients among different numbers of stenotic vessels with CAD

	0 (n = 30)	1 (n = 215)	2 (n = 170)	3 (n = 184)	P
Male (%)	50	61.6	62.9	60.3	0.594
Age (years)	60.77±10.99	60.55±10.48	62.69±9.70	64.60±10.21	0.001
Hypertension (%)	40	40.3	44.1	50.5	0.209
Diabetes mellitus (%)	20	16.2	20	20.7	0.663
BMI (Kg/m^2)	29.14±2.18	24.66±4.41	24.90±3.32	24.87±4.17	0.185
TC (mmol/l)	4.70±1.12	4.93±1.16	4.93±1.24	4.96±1.22	0.779
TG (mmol/l)	1.95 (1.34-2.60)	1.69 (1.06-2.71)	1.60 (1.14-2.29)	1.62 (1.10-2.62)	0.702
LDL-C (mmol/l)	2.71±0.91	2.99±0.88	3.10±0.95	3.05±1.00	0.273
HDL-C (mmol/l)	1.23±0.40	1.21±0.36	1.23±0.33	1.19±0.34	0.767
Serum creatinine (μmol/L)	80.67±16.53	80.96±13.79	81.13±21.10	86.75±38.59	0.147
Serum uric acid (μmol/L)	311.38±107.32	332.36±111.16	337.80±119.25	340.98±109.40	0.657
Hemoglobin level (g/l)	134.15±10.84	137.99±21.41	135.68±17.88	131.26±23.65	0.023
RDW (fl)	44.50±3.92	45.67±9.36	48.58±3.98	46.44±4.91	0.458
PDW (fl)	16.23±0.41	16.32±0.47	16.39±0.56	16.26±0.58	0.117
LVEDP (mmHg)	8.77±6.01	9.96±4.68	11.36±5.39	11.93±6.01	<0.001
Gensini score	7.75 (3.75-12.25)	15.5 (10.0-26.37)	33.75 (22.88-53.5)	73.25 (42.12-102.75)	<0.001

Continuous data are presented as mean ± SD and/or median (25% to75%), percentages are used to express categorical variables. CAD = coronary artery disease, BMI = body weight (kg)/body height^2 (m^2), TC = Total Cholesterol, TG = blood Triglycerides, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, RDW = red blood Cell distribution width, PDW = platelet distribution width, LVEDP = left ventricular end-diastolic pressure.

0, 1, 2, or 3 according to the number of major coronary vessels.

Gensini scoring

The severity of CAD was determined by Gensini scoring [11]. The Gensini score (GS) is computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. Reductions in the lumen diameter of 25%, 50%, 75%, 90%, 99% and complete occlusion were given Gensini score of 1, 2, 4, 8, 16 and 32, respectively. Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment, that is, the LM was assigned the significant multiplier × 5; the proximal segment of the LAD × 2.5; the proximal segment of the LCX × 2.5; the mid segment of the LAD × 1.5; the RCA, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery × 1; and others × 0.5.

Statistical analysis

Continuous data are presented as mean ± SD and/or median (25% to 75%), while percentages were used to express categorical variables. The conformity of data with a normal distribution was analyzed using a Kolmogorov-Smirnov

test. Categorical variables of subjects were analyzed by the chi-square test. One-way analysis of variance (ANOVA) or Kruskal-Wallis H tests were used to compare the 3 groups. Differences in continuous variables between 2 groups were determined by t test or Mann-Whitney U test. Spearman correlation coefficients were evaluate the linear correlation between LVEDP and correlated variable. Multivariate logistic regression was used to determine factors affecting CAD. A linear regression analysis was applied to determine the correlation between LVEDP and Gensini score. The SPSS (version 13.0, Chicago, IL, USA) was used to perform all statistical data. All analyses were 2-sided and significance was established at the 0.05 level.

Results

Comparisons of patients with and without CAD

The characteristics of study subjects are listed in **Table 1**. There were 313 patients without CAD and 599 patients with CAD according to CAG results. CAD patients were significantly older, more frequently in male, hypertension and diabetes, lower HDL-C, higher serum creatinine, serum uric acid, GS and LVEDP (9.58±5.78 mmHg vs 10.9±5.46 mmHg, *P*<0.001). There were no significant difference in BMI, TC, TG,
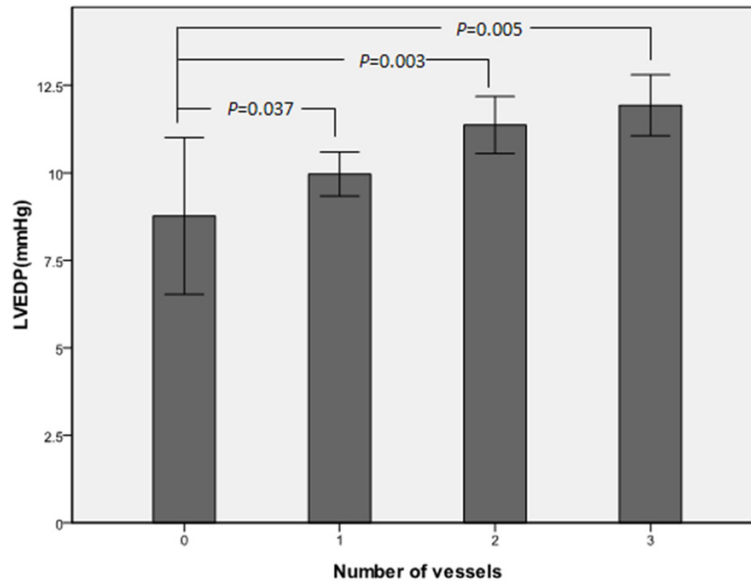
Figure 1. Comparisons of LVEDP in terms of number of vessels (n = 0, 215, 170, and 184, respectively in 0, 1, 2, and 3-vessel groups). CAD = coronary artery disease, LVEDP = left ventricular end-diastolic pressure.

Table 3. Variables affecting CAD according to the multivariate logistic regression model

	OR	95% CI	P
Sex	2.08	1.46-2.95	<0.001
Age (per 1 year)	1.04	1.02-1.05	<0.001
Diabetes mellitus	0.37	0.21-0.62	<0.001
Hypertension	1.03	0.73-1.45	0.85
LVEDP (per 5 mmHg increase)	1.11	1.02-1.29	0.02
HDL-C (per 1 mmol/l increase)	0.55	0.35-0.85	0.009
Serum creatinine (per 10 µmol/L increase)	1.01	0.95-1.06	0.7
Serum uric acid (per 10 µmol/L increase)	1	0.99-1.02	0.47

CAD = coronary artery disease, HDL-C = high-density lipoprotein cholesterol, LVEDP = left ventricular end-diastolic pressure.

increase of number of vessels (**Figure 1**).

Factors influencing CAD development

The variables which were significantly different in CAD and non-CAD groups, containing age, sex, hypertension, diabetes, HDL-C, serum creatinine, serum uric acid, and LVEDP, were admitted into the multivariate logistic regression. The results were listed in **Table 3**. Age, sex, diabetes, HDL-C and LVEDP (OR = 1.11, per 5 mmHg increase, 95% CI 1.02-1.29, *P* = 0.02) were correlated independently with the presence of CAD.
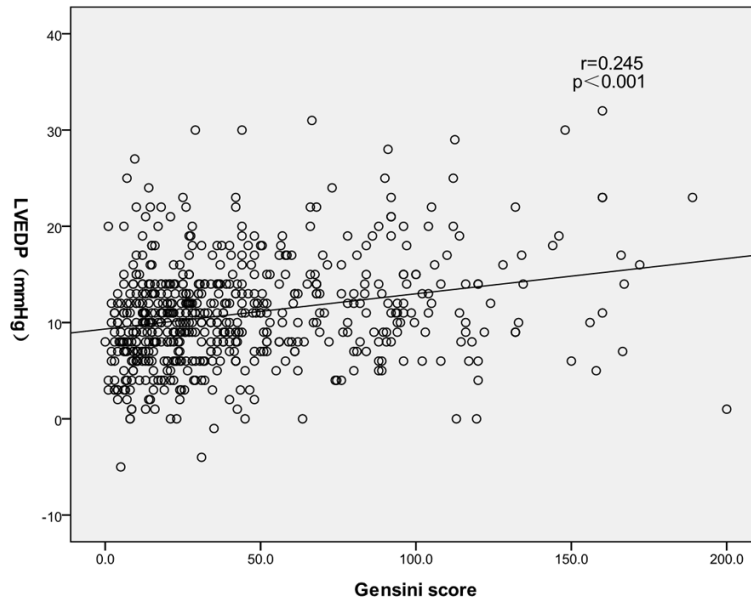
In CAD groups, Spearman's correlation analysis showed that LVEDP was positively correlated with Gensini score (r = 0.245, *P*<0.001). The correlation between LVEDP and GS was showed in **Figure 2**. By multivariate linear regression analysis, after adjusted for age, sex, hypertension, diabetes, TG, TC, HDL-C, LDL-C, serum creatinine, uric acid, hemoglobin level, RDW and PDW, LVEDP was also significantly associated with GS (standardized β = 0.034, *P* = 0.001).

LDL-C, hemoglobin level, RDW, PDW between the two groups.

Relation between vessels and CAD as well as its extent

The CAD were divided into four subgroups according to the number of vessels, coding as 0-vessel, 1-vessel, 2-vessel, 3-vessel. The variables in different subgroups are presented in **Table 2**. There were 30 patients in 0-vessel group, 215 in 1-vessel group, 170 in 2-vessel group, 184 in 3-vessel group. There were significant difference among hemoglobin level, LVEDP and GS. LVEDP was increased with an

In non-CAD group, LVEDP was only correlated with age (r = 0.123, *P* = 0.030), while not correlated with other variables in this study.

Discussion

The present study showed that LVEDP was significantly associated with CAD as well as its severity and extent. This was the first study to investigate the association between LVEDP measured by left cardiac catheterization and CAD as well as its severity and extent evaluated by coronary angiography (CAG). The results displayed that there was significant difference of LVEDP between CAD and non-CAD group, more-

Figure 2. Spearman correlation analysis shows the correlation between LVEDP and Gensini score in CAD patients r = 0.245, *P*<0.001. CAD = coronary artery disease, LVEDP = left ventricular end-diastolic pressure.

over, LVEDP was independently associated with CAD. In different subgroups, LVEDP was increased with an increase of number of stenotic vessels. Spearman's correlation analysis showed that LVEDP was positively correlated with Gensini score. In non-CAD group, LVEDP was only correlated with age, not GS.

Diastole is an energy-dependent process [12], thus, adequate energy supply must be available for this process to occur. During myocardial ischemia, the energy supply is reduced or abolished. Diastolic function has a lower injury threshold than systolic function, therefore, diastolic dysfunction precedes the onset of systolic dysfunction and persists longer than systolic disturbance in ischemia [13]. High myocardial stiffness in ischemic zones is increased with CAD patients [12]. During ischemia, increased myocardial stiffness in addition to a decreased rate of wall thinning and slow active pressure decay contribute to the upward shift in left ventricular pressure-wall thickness and pressure-volume relationships, which lead to elevated LVEDP [14]. Therefore, CAD has an increased susceptibility to DD. The present study showed that CAD patients had higher LVEDP than non-CAD. And LVEDP was independently associated with CAD.

With the development of researches, people pay more and more attention to DD. The preva-

lence of pre-clinical diastolic function in the general adult population is approximately 20% to 30%, with increasing age, CAD, cardiovascular comorbidities, and diabetes, which were independent risk factors for development of DD [15]. DD refers to abnormal mechanical properties of the myocardium and includes abnormal left ventricular diastolic distensibility, impaired filling, chamber stiffness, and slow or delayed relaxation [16]. In terms of physiology, any mechanism that interferes with actin-myosin cross-bridge detachment or with removing calcium from the cytosol can delay the relaxation [17]. DD is at higher risk of developing HFpEF, and the risk of progression to HFpEF appears to be higher among those with hypertension, renal dysfunction, diabetes, anemia, or CAD. Ren et al. [18] reviewing 693 subjects with CAD found that 36% had mild to severe left ventricular DD. They also found that the presence of moderate to severe left ventricular DD was strongly predictive of hospitalization for heart failure and death from heart disease. Ongoing ischemia can lead to diastolic wall motion abnormality [19]. Indeed, we should be aware of the presence of DD in CAD patients.

Consistent with the present study, Lin et al. [20] showed that extent and severity of obstructive as well as nonobstructive CAD by coronary CT angiography are associated with increased LVEDP. The present study also listed that LVEDP was increased with an increase of number of vessels and positively correlated with Gensini score. The previous study showed that there was a striking correlation between the severity degree of CAD and the decrease of left ventricular compliance [21]. Paul et al. [22] showed that induced left ventricular diastolic impairment persists for a prolonged period after resolution of the ischaemic episode. The incidence and magnitude of the DD are determined by the severity of the ischaemia. Conversely, abnormal diastolic function can also predicts the severity of ischemia. Perrone-Filardi et al. [23] displayed that among patients with CAD and with normal left ventricular systolic function at

rest, impaired left ventricular filling and regional asynchrony predict a greater degree of ischemia, suggesting a greater extent of jeopardized myocardium. Other study also observed that patients with impaired LV relaxation had more severe CAD [24]. However, Abalı et al. [25] showed that the diastolic function did not demonstrate any impairment according to the severity of the CAD in patients. Nevertheless, the diastolic function was evaluated by echocardiography in the study of Abalı G et al., the predictive capacity of E/Em for elevated left ventricular diastolic pressures was weak. Because mitral flow is dependent on multiple interrelated factors, it has not been possible to determine diastolic function from the mitral flow velocity curves in many subsets of patients [26, 27].

The present study also demonstrated that LVEDP was only correlated with age, not GS in non-CAD group. Aging alter left ventricular diastolic function with high LV stiffness, increased myocardial fibrosis, reduced rate and extent of the rapid filling phase related to increased regional diastolic asynchrony, and then lead to impaired left ventricular diastolic function [28]. So we should pay attention to the underlying diastolic dysfunction in elderly in clinical.

Different with other studies, LVEDP ≥15 mmHg was 17.3% in the whole patients, and 19.3% in the CAD patients. Although the incidence of diastolic dysfunction was not high. LVEDP was significant association with CAD as well as its extent and severity. Indeed, doctors should concerned the diastolic function in patients, especially the CAD patients.

These study findings may have important potential clinical and therapeutic implications. DD precedes the onset of systolic dysfunction in ischemia, so we should be aware of the presence of CAD in patients with normal left ventricular ejection fraction but shortness of breath. During the procedure of CAG, if the stenosis of coronary artery is serious, the left cardiac catheterization should be performed to evaluate the diastolic function additionally if admitted. By which, the underlying diastolic dysfunction can be identified as early as possible, avoiding the development of HFpEF and other adverse events. Considering the treatment of DD, the SWEDIC study [29] showed that carvedilol resulted in echocardiographic

improvements in patients with HFpEF. The RALI-DHF trial [30] demonstrated that ranolazine infusion significantly reduced LV end diastolic pressure from 21.3 to 19.1 mmHg and improved hemodynamic measurements such as pulmonary capillary wedge pressure. Future studies are needed to investigate the optimal therapeutic methods of diastolic dysfunction. The present study did not involve the therapeutic measurement of DD.

Limitations

The study was a retrospective analysis, cannot avoiding selection bias. The patients enrolled in this study were all with clinical suspicion of CAD, not containing the asymptomatic myocardial ischemia patients. Although we included measured covariates, there are still unknown confounders may affect the results. Evaluation of CAG were by different interventional physicians, which leading to mildly different with results of CAG.

Conclusion

Elevated LVEDP was significantly associated with CAD as well as its extent and severity. LVEDP was only correlated with age, not GS in non-CAD patients. LVEDP measurement provides incremental clinical value for CAD and non-CAD patients.

Disclosure of conflict of interest

None.

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